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Pesticide Fact Sheet Number 155: Metalaxyl

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This document contains up-to-date chemical information, including a summary of the Agency's regulatory position and rationale, on a specific pesticide or group of pesticides. A Fact Sheet is issued after one of the the following actions has occurred.

1. Issuance or reissuance of a registration standard,
2. Issuance of each special review document,
3. Registration of a significantly changed use pattern,
4. Registration of a new chemical, or
5. An immediate need for information to resolve controversial issues relating to a specific chemical or use pattern.

17. Document Analysis a. Descriptors

Pesticides, regulations, Chemical Information Fact Sheet, Use Patterns, science findings.

b. Identifiers/Open-Ended Terms

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EPA

Pesticide Fact Sheet

Name of Chemical: METALAXYL
Reason for Issuance: REGISTRATION STANDARD
Date Issued: MARCH 1988
Fact Sheet Number: 155

DESCRIPTION OF CHEMICAL

Generic Name: N-(2,6-Dimethylphenyl)-N-(Methoxyacetyl) Alanine Methyl ester.
Common Name: Metalaxyl
Trade Names: Ridomil, Subdue, Apron, Proturf.
EPA Shaughnessy Code: 113501
Chemical Abstracts Service (CAS) Number: 57837-19-1
Year of Initial Registration: 1979
Date of Initial Registration Standard: December 1981
Pesticide Type: Systemic Fungicide
U.S. and Foreign Producers: Ciba-Geigy, O.M. Scott and Son, Co. Wilbur-Ellis, and Gustafson.

USE PATTERNS AND FORMULATIONS

Application Sites: Metalaxyl is registered for use on over 100 agricultural crops (including more than 30 seed treatment uses). Metalaxyl is also registered for ornamental and turf uses.

Major Uses: More than 90% of the total poundage of metalaxyl used domestically is used in the following ten crops/sites: tobacco, turf, potatoes, ornamentals, soybean (seed treatment), onions, citrus, cucurbits, tomatoes, and cotton.

Application Rates: Metalaxyl is applied to soil or foliage. Application rates range from 0.135 to 8.0 lb ai/acre for agricultural crops, from 0.25 to 1.12 oz ai/100 lb seed for agricultural seed treated, from 0.33 to 1.35 lb/ai/acre for ornamental turf, and from 0.90 to 7.20 lb/ai acre for ornamental trees and plants. Multiple applications (varying with use) are approved.

Method of Application: Foliar application; soil application by incorporation, surface spraying (broadcast or band), drenching, sprinkler or drip irrigation; soil mixing; trunk spraying. For agricultural seed treatment metalaxyl is applied with conventional slurry or mist seed treating equipment.

Types Registered: Single active ingredient products containing metalaxyl are formulated as a granular (G), pelleted/tableted (P/T) (in fertilizer spikes), wettable powder (WP), emulsifiable concentrate (EC), and flowable liquid concentrate (FlC), as well as a 90% technical product. The granular, wettable powder and emulsifiable concentrate formulations are also formulated as multiple active ingredient products. In addition, metalaxyl is sold in a combination with mancozeb, chlorothalonil, pentachloronitrobenzene, captan, and triadimefon.

SCIENCE FINDINGS

Summary of Science Statements

Studies indicate that metalaxyl is not oncogenic or teratogenic. Studies also indicate that metalaxyl does not cause increased incidence of tumors or cause embryotoxic, fetotoxic or teratogenic effects. Metalaxyl also does not cause reproductive effects nor did it induce gene mutations in bacteria, yeast, and mouse lymphoma cells and does not cause chromosomal aberrations in tests with yeast, hamsters, and mice.

Metalaxyl was found to be practically nontoxic acutely and subacutely to avian species and to present no adverse effects to avian and mammalian populations. Metalaxyl poses no hazard to endangered terrestrial or aquatic animal species or to plant species.

Physical/Chemical Characteristics

Technical

Physical State:	Crystalline
Color:	White to beige
Odor:	Odorless
Solubility:	Water - 00.7%
	Benzene - 55.0%
	Hexane - 00.9%
	Methanol - 65.0%
	Isopropanol - 27.0%
	Methylene Chloride - 75.0%
Stability:	Stable up to 300°C; slight exothermic reaction up to 450°C
Melting Point:	71 - 72°C
Vapor Pressure:	2.2×10^{-6} Torr at 20°C
Density:	1.21 g/cm^3 at 20°C

Toxicology Profile

Acute Toxicity:

o Acute Oral Toxicity	Toxicity Categoty III (moderate acute oral)
(Rat): 669 mg/kg (Mice): 788 mg/kg (Hamster): 7120 mg/kg	
o Acute Dermal Toxicity	Toxicity Category III (moderate acute dermal)
(Rabbit): >6000 mg/kg (Rat): >3170 mg/kg	
o Primary Eye Irritation	Toxicity Category II (moderate eye irritant)
(Rabbit): No effect	
o Primary Skin Sensitization	Toxicity Category IV (slight skin irritant)
(Rabbit): slight effect	
o Primary Dermal Sensitization	Toxicity Category IV (not a sensitizer)
(Guinea Pig): No effect	

Subchronic Feeding Studies

Rodent Feeding Studies

In 90-day feeding studies in rats and mice the liver was the target organ for metalaxyl toxicity.

In female rats a NOEL of 250 ppm (12.5 mg/kg/day) and a lowest-observed effect level (LOEL) of 1250 ppm (6.25 mg/kg/day) were observed.

In male mice, a NOEL of <1250 ppm (187.5 mg/kg/day), and a LOEL of 1250 ppm (6.25 mg/kg/day) were observed.

Non-Rodent Feeding Study

A 90-day feeding study in dogs showed no toxicity up to 1250 ppm in their diet (31.25 mg/kg/day; highest dose tested).

Subchronic Dermal Toxicity

Metalaxyl had no effect on rabbits when applied to intact or abraded skin for 21 days at doses up to 1000 mg/kg/day.

Subchronic Inhalation Toxicity

No effects were observed in rats exposed to smoke from cigarettes containing metalaxyl. The NOEL in this study is greater than 13,000 ppm (highest dose tested).

Chronic Toxicity

Metalaxyl had minimal effects in chronic feeding studies with rats and dogs. The NOEL established in rats was 250 ppm (12.5 mg/kg/day), and the LOEL was 1250 ppm (62.5 mg/kg/day). In dogs the LOEL was established at 1000 pppm (250 mg/kg/day), and the NOEL was 250 ppm (62.5 mg/kg/day).

Oncogenicity

The long-term feeding studies in rats and mice showed no increase in the incidence of tumors as a result of metalaxyl.

Teratology

In pregnant rats, NOEL's for maternal and developmental toxicity were established at 50 mg/kg/day, and LOEL's for both types of toxicity were established at 250 mg/kg/day.

Metalaxyl caused no embryotoxic, fetotoxic, or teratogenic effects in treated rabbits. The NOEL for maternal toxicity was 300 to 500 mg/kg/day, and the developmental toxicity was greater than 300 mg/kg/day (highest dose tested in the main study).

Reproduction

In a multi-generation reproduction study with rats, no dose-related effects were observed throughout the three generations with respect to toxicity or reproductive parameters. The NOEL for reproductive and developmental toxicity is greater than 1250 ppm (12.5 mg/kg/day).

Mutagenicity

Metalaxyl did not induce gene mutations in bacteria, yeast and mouse lymphoma cells in vitro with or without metabolic activation. The fungicide also caused no structural or numerical chromosomal aberrations as indicated by yeast, hamsters or mice. No DNA damage was observed in bacteria and no unscheduled DNA synthesis was noted in rat primary hepatocytes or human fibroblasts in vitro as the result of exposure to metalaxyl. These results suggest that metalaxyl is not genotoxic.

Metabolism

Metabolism studies in rats showed that single oral doses of metalaxyl are readily absorbed. Approximately 62 to 65% of

the administered radioactivity is recovered in the urine and feces within 24 hours after dosing, and 96% is recovered during the 48 hours after dosing. The major route of excretion in males was the feces after oral and dermal doses, while that for females was the urine for both routes of administration. The distribution of radiolabel observed six days after dosing did not indicate that metalaxyl residues were stored in tissues following a single dose.

Dermal Absorption

The absorption $T_{1/2}$ values for metalaxyl in tetrahydrofuran (THF) ranged from 12 hours (in male rats receiving a 1 mg/kg dermal dose) to 20 hours (male rats given a dermal dose of 10 mg/kg). The value for females was 13 hours for both doses.

ECOLOGICAL CHARACTERISTICS

Metalaxyl has been found to be practically nontoxic acutely and subacutely to avian species and to present no adverse effects to avian and mammalian populations. There is no indication of detrimental effects on aquatic plant species and the technical pesticide is practically nontoxic to freshwater aquatic animal species. The most sensitive organism appears to be Daphnia magna, having LC_{50}s of 28 and 12.5 ppm with technical and formulated pesticides, respectively.

Chronic toxicity assays on aquatic species and fish accumulation testing do not suggest that metalaxyl presents a long-term risk in the aquatic environment. It appears very unlikely that metalaxyl could accumulate in water or sediments to concentrations that would pose a risk to aquatic populations.

Although use of metalaxyl presents little risk to freshwater populations it cannot be assumed that the same holds true for marine/estuarine species which may be exposed in connection with several of the registered uses. The Agency is requesting data on marine/estuarine species such as oysters and shrimp.

Endangered Species

The registered uses of technical metalaxyl and a widely used formulation, Ridomil® 27.9% ai EC (which appears to be more toxic to aquatic species than the technical), do not present a hazard to endangered terrestrial or aquatic animal species or plant species.

Environmental Fate

Metalaxyl was found to be moderately stable under normal environmental conditions. Fish accumulation was found not to exceed 7X when fish were exposed to metalaxyl at 1 ppm in water, and the residues were found to accumulate in the nonedible portions over the edible portions. Residues declined rapidly during depuration.

The rotational crop data demonstrated the need for a 12-month rotational crop restriction because some crops will take up metalaxyl residues of concern when planted 12 months or more after treatment of a prior crop. Confined studies are needed to identify all residues of concern plus field tests are necessary to determine the need for additional tolerances.

In addition, ground water monitoring studies were required early in the registration process for metalaxyl. While subsequent submissions were judged to be sufficient at the time, these studies are no longer adequate and further data are required.

TOLERANCE REASSESSMENT

Tolerances have been established for residues of metalaxyl in numerous varieties of raw agricultural commodities (40 CFR 180.408) and also in food and feed commodities (21 CFR 193.277 and 21 CFR 561.273, respectively). In addition, tolerances have also been established for indirect or inadvertant residues of metalaxyl.

The acceptable daily intake (ADI) is based on the six month feeding study in dogs (NOEL of 6.3 mg/kg/of body weight/day) and a 100-fold safety factor. Therefore, the ADI is calculated to be 0.063 mg/kg/day.

REGULATORY POSITION

This review of metalaxyl is the second intensive evaluation of the compound. A Registration Standard was developed in 1981 in conjunction with its initial registration. At that time metalaxyl was registered for non-food uses on tobacco, conifers, ornamentals, and turf and was not registered for any food or feed uses. The only additional data needed to support the registered non-food uses in 1981 were groundwater monitoring, subchronic inhalation toxicity, phytotoxicity and storage stability. Since the issuance of the 1981 Registration Standard, registrations have been approved for use on over 100 agricultural crops. These registrations were granted based on adequate supporting data (including residue, acute and chronic data) at the time of application for registration.

In 1984, the Agency promulgated general rules at 40 CFR Part 158, which set forth the range of data which must be submitted to EPA to support the registration or reregistration of each pesticide under FIFRA. Based on these revised and expanded data requirements, the toxicity data base for metalaxyl is still virtually complete and in most cases is adequate to support continued registration of existing uses. However, some data determined to support registration in the past only partially fullfill current data requirements. As a result, several studies primarily in the disciplines of residue chemistry and environmental fate, must be conducted and submitted to the Agency. In addition, several new data requirements are being imposed to characterized potential adverse effects to marine/estuarine species.

The following Agency positions are based on the substantially complete data base currently available for metalaxyl:

- Metalaxyl is not being placed in Special Review at this time because none of the risk criteria listed in 40 CFR 154.7 prescribing a Special Review have been met.

- The Agency is requesting rotational crop studies and, in order to meet the statutory standard for continued registration, product labeling must bear a 12-month rotational crop restriction as an interim measure.

- Additional ground water monitoring and laboratory leaching studies are being required. The Agency has determined that data submitted on ground water monitoring are inadequate.

- Ground water monitoring data will be reviewed when submitted in order for the Agency to determine whether further regulatory action is warranted based on this concern.

- The Agency is requiring further data on potential adverse effects to marine/estuarine species to determine if currently registered uses will result in exposure levels of concern to these populations.

- While data gaps are being filled, currently registered manufacturing-use products (MP's) and end use products (EP's) containing metalaxyl as the sole active ingredient may be sold, distributed, formulated, and used, subject to the terms and conditions specified in this Standard. However, registrants must provide or agree to develop additional data, as specified in the Data Appendices, in order to maintain existing registrations.

LABELING REQUIREMENTS

All metalaxyl products must bear appropriate labeling as specified in 40 CFR 162.10. Appendix II of the Standard contains information on label requirements.

In order to remain in compliance with FIFRA, no pesticide product containing metalaxyl may be released for shipment by the registrant after April 30, 1989, unless the product bears amended labeling which complies with the specifications in the Standard.

In order to remain in compliance with FIFRA, no pesticide product containing metalaxyl may be distributed, sold, offered for sale, held for sale, shipped, delivered for shipment, or received and (having been so received) delivered or offered to be delivered by any person after April 30, 1990, unless the product bears amended labeling which complies with the specifications of the standard.

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In addition to the above, in order to remain in compliance with FIFRA, the Agency is requiring:

- Revised environmental hazard labeling
- 12-month rotational crop statement

SUMMARY OF MAJOR DATA GAPS

40CFR§158.120 - Product Chemistry
- Description of Beginning Materials and Manufacturing Process
- Discussion of the Formation of Impurities
- Preliminary Analysis
- Certification of Ingredient Limits
- Analytical Methods to Verify Certified Limits

40CFR§158.125 - Residue Chemistry
- Nature of the Residue in Livestock
- Residue Analytical Method
- Storage Stability Data
- Magnitude of the Residue (potatoes; sugar beet roots; soy beans; cereal grains; forage, fodder and straw of cereal grains; cottonseed; hops; peanuts; pineapples; sunflower seed)

40CFR§158.130 - Environmental Fate
- Photodegradation Studies in Water
- Terrestrial Field Dissipation Studies
- Confined Accumulation Studies on Rotational Crops
- Field Accumulation Studies on Rotational Crops
- Ground Water Monitoring and Laboratory Leaching Studies

40CFR§158.135 - Toxicology
- Acute Inhalation Toxicity
- Metabolism Studies

40CFR§158.145 - Ecological Effects
- Acute LC_{50} Estuarine/Marine Organisms (shrimp and oyster)

CONTACT PERSON AT EPA:

Lois A. Rossi
Product Manager (21)
Fungicide-Herbicide Branch
Registration Division (TS-767C)
Office of Pesticide Programs, EPA
Washington, D.C. 20460

Telephone: (703) 557-1900

DISCLAIMER: The information in this Pesticide Fact Sheet is a summary only and is not to be used to satisfy data requirements for pesticide registration and reregistration. The complete Registration Standard for the pesticide may be obtained from the contact person listed above.